REMARKS

This Reply is responsive to the Office Action dated September 23, 2003. Entry of the amendments and remarks submitted herein and reconsideration of the claimed subject matter pursuant to 37 CFR §1.116 is respectfully requested.

I. Status of the Claims

Claims 1, 5 and 20-39 were pending in this application at the time of the Office Action dated January 15, 2003. Claims 1, 5, 20-31, 33, 35 and 39 were withdrawn from consideration. As a result of this amendment, claims 36-38 have been canceled. Accordingly, claims 32 and 34 are now pending and under examination.

II. Amendments to the Claims

Without prejudice to future prosecution, claims 36-38 have been canceled above in order to expedite allowance. In addition, claim 34 has been amended to delete reference to the c-erg gene, which is now recited in amended claim 32. Claim 32 has been amended to indicate that the claimed pharmaceutical composition is suitable for injection or oral administration. Support for this amendment may be found on page 14, lines 18-20. No prohibited new matter has been added by way of these amendments.

III. Rejection Under 35 U.S.C. §102

Claims 32, 34 and 36-38 stand rejected under 35 U.S.C. §102(b) as being allegedly anticipated by Dhordain *et al.* Essentially, it is the Examiner's position that the erg gene composition of Dhordain *et al.* is indistinguishable from Applicants' claimed

compositions notwithstanding the fact that Applicants' compositions are pharmaceutical compositions. Further, the Examiner believes that the nucleic acid probe taught in the Dhordain reference inherently anticipates the nucleic acids recited in claims 36-38. Applicants respectfully traverse the rejection as it applies to the amended claims above.

At the outset, Applicants respectfully note that claim 34 has been amended to delete reference to the c-erg gene. Accordingly, the rejection of claim 34 over the Dhordain reference may be withdrawn. In addition, without necessarily agreeing with the rejection, Applicants have cancelled claims 36-38 to expedite allowance. Accordingly, the rejection with respect to claims 36-38 may also be withdrawn.

Claim 32 has been amended to indicate that the claimed composition is suitable for injection or oral administration. Applicants respectfully submit that the amended claim is distinguishable from any composition disclosed in the Dhordain reference, since Dhordain does not teach a pharmaceutical composition suitable for injection or oral administration. Rather, as the Examiner acknowledges in the Office Action, Dhordain is concerned with the cloning of the c-erg gene. While the cloned gene was transfected into NIH3T3 cells (see p. 27, col. 1), transfection was performed by a lipofection method, which employs reagents that are not suitable for *in vivo* use (see, for instance, the Lipofectamine™ Reagent sheet attached hereto, stating that the reagent is suitable for transfection into cultured eukaryotic cells). Further, there is no suggestion in Dhordain that the c-erg gene might be useful for the treatment of any disorder. Thus, Dhordain neither teaches nor suggests pharmaceutical compositions comprising the disclosed c-erg gene that are suitable for injection or oral administration as recited in amended claim 32.

The Board of Patent Appeals and Interferences has addressed, and reversed, similar rejections on many occasions. Applicants have attached a sample of three cases hereto for the Examiner's consideration. For instance, in *Ex parte Clark et al.*, the Examiner rejected a claim to a pharmaceutical composition under 35 U.S.C. §§102(b) and 103, asserting that the prior art products inherently possessed the characteristics of the claimed product. The Board reversed the rejection, emphasizing that the rejected claim required that the recited protein be "in combination with" a pharmaceutically acceptable vehicle, and that the Examiner had not acknowledged or discussed this aspect of the invention (see p. 5 of decision).

Similarly, in *Ex parte Cole et al.*, the Examiner had rejected claims to pharmaceutical compositions under 35 U.S.C. §§102(b) and 103, asserting that the product recited in the claims was in the prior art. The Board reversed the rejection, emphasizing that the Examiner had not pointed out where the cited reference teaches the product in combination with a pharmaceutically acceptable carrier, or that the product is in pharmaceutically acceptable form, and it was not apparent where the cited reference discloses each of these limitations (pp. 3-4 of decision).

In *Ex parte Charoenvit et al.*, the Examiner rejected claims to an antibody formulation in a pharmaceutically suitable injectable solution under 35 U.S.C. §103, asserting that it would be obvious to formulate the recited antibodies as disclosed in the primary reference in a pharmaceutically acceptable diluent as disclosed in the secondary reference. The Board reversed the rejection, noting that the combined references would not have led the skilled artisan to a pharmaceutically acceptable formation as claimed,

and that there was no evidence of record supporting a reasonable expectation of success for the use of the recited antibody in a pharmaceutical formulation (p. 12 of decision).

As noted above, amended claim 32 is directed to a pharmaceutical composition comprising a c-erg gene that is suitable for injection or oral administration. Dhordain *et al.* neither teaches nor suggests pharmaceutical compositions comprising the disclosed c-erg gene that are suitable for injection or oral administration as recited in amended claim 32. Given the amendment to the claim and the various decisions of the Board discussed above, withdrawal of the rejection of claim 32 under 35 U.S.C. §102(b) is respectfully requested.

IV. Rejections Under 35 U.S.C. §112

Claims 32 and 34 stand rejected under 35 U.S.C. §112, first paragraph as allegedly containing subject matter which was not described in the application in such a way as to enable one skilled in the art to make and/or use the invention. Essentially, the examiner has dismissed the abstracts provided by Applicants showing that the skilled artisan would consider the *in vitro* osteoblast model to be representative of *in vivo* function, asserting that the issue is instead how to effectively deliver erg or C-11 DNA to a cell in order to get an effective response. Further, the Examiner dismisses U.S. Patent 5,580,859 cited by Applicants as evidence that direct injection of naked nucleic acid molecules into muscle results in high levels of expression, asserting that the '859 patent does not claim or provide examples of any method of treatment by DNA injection. Applicants respectfully traverse the rejection.

At the outset, Applicants respectfully note that the pending claims are directed to pharmaceutical compositions rather than methods of treatment. Pharmaceutical compositions may be employed at several stages in the development of a method of treatment, for instance during clinical trials or animal models. Accordingly, the examiner's assertion that the '859 patent does not disclose methods of treatment appears to be misplaced given that the claims are directed to pharmaceutical compositions. The '859 patent teaches the injection of pharmaceutically acceptable DNA formulations, and is therefore relevant to the instant claims.

In any case, as exhibited by the '859 patent, it was well known prior to the filing of this invention that direct injection of naked nucleic acids into the muscle or skeletal muscle results in high levels of expression of injected genes, via uptake of the nucleic acids into cells in the vicinity. Further, Applicants have shown by the submission of several reference abstracts that calcification of osteoblasts *in vitro* is a recognized model for identifying compounds that modulate the calcification process *in vivo*. These teachings, in combination, would enable the skilled artisan to transfer Applicants' *in vitro* functional results to an *in vivo* setting without undue experimentation.

The Examiner asserts that the specification does not teach what kind of vector to use for administration, how much DNA should be injected, where the DNA should be injected or how much gene expression would be necessary to affect treatment. Yet these are parameters that the skilled artisan, having an expectation of success based on Applicants' disclosure, would routinely optimize depending on the patient to be treated and the location and severity of disease. Indeed, according to the Federal Circuit, a considerable amount of experimentation is permissible, if it is merely routine. *In re*

Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Angstadt*, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)). Further, the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm"n 1983), *aff'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985).

The Board of Patent Appeals and Interferences supports the use of *in vitro* models to enable methods of therapy. For instance, in *Ex parte Siler-Khodr* (decision submitted herewith), the Examiner rejected therapy claims for lack of enablement because the specification did not "tell how to use the *in vitro* methods in a patentable manner" (see p. 5 of decision). The Examiner further argued that, although the *in vitro* tests provided information for further scientific research, particularly *in vivo*, they did not enable the use of the recited compound for the indicated treatments *in vivo*. The Board reversed the rejection, noting that, although the Examiner had presented a *prima facie* case of lack of enablement, the rejection should have been withdrawn once Applicants submitted publications showing the acceptability of the *in vitro* model as representative of *in vivo* results to those of ordinary skill in the art (see pp. 6-7). The Board further noted that, due to legal and ethical considerations, often *in vitro* testing is the best possible system for demonstrating therapeutic potential (p. 7). As stated on p. 9 of the decision:

> *In vitro* results with respect to the particular pharmacological activity are generally predictive of *in vivo* test results, *i.e.*, there is a reasonable correlation therebetween. Were this not so, the testing procedures of the pharmacological industry would not be as they are. It is not urged that there is an invariable exact correlation between *in vitro* test

> results and *in vivo* test results. *Cross v. Iizuka*, 753 F.2d 1040, 1044, 224 USPQ 739, 742 (Fed. Cir. 1985); *Nelson v. Bowler*, 626 F.2d 853, 856, 206 USPQ 881, 883 ([CCPA] 1980). It is appellant's position that successful *in vitro* testing for a particular pharmacological activity establishes a significant probability that *in vivo* testing for this particular pharmacological activity will be successful. On the facts before us, we agree.
>
> Based upon the relevant evidence as a whole, we find there to be a reasonable correlation between the disclosed *in vitro* utility and an *in vivo* activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence. *Cross v. Iizuka, supra; Nelson v. Bowler, supra.*

Thus, Applicants have demonstrated the known correlation between the *in vitro* testing reported in the specification and *in vivo* activity by reference to article abstracts. As evidenced by the case law cited above, the Board has endorsed the suitability of *in vitro* testing as providing adequate enablement where the evidence of record shows a reasonable correlation between *in vitro* utility and *in vivo* activity. Further, Applicants have pointed to U.S. Patent 5,580,859 as evidence that it was well known in the art at the time of filing that local injection of pharmaceutically acceptable DNA formulations into the muscle or skeletal muscle results in high levels of gene expression. With routine optimization, the skilled artisan would have been able to use the claimed pharmaceutical compositions *in vivo* without undue experimentation based on the results reported in the specification and the knowledge in the art regarding injection delivery of DNA.

The Examiner appears to dismiss the '859 patent in view of the teachings in Nishikawa *et al.* (Human Gene Therapy, 2001). According to the Examiner, Nishikawa *et al.* disclose that the uptake of plasmid DNA by muscle cells is relatively inefficient, and that target-specific gene transfer is difficult to achieve. Applicants respectfully submit that, while Nishikawa *et al.* may have observed low efficiency with their

particular study, their results are far from representative. In fact, the scientific literature is replete with successful reports of intramuscular gene therapy since the issuance of the '859 patent. Applicants have attached a few representative abstracts to this Reply for the Examiner's consideration, which show successful application of intramuscular gene therapy in disease models for angiogenesis, heart disease, type 1 diabetes, and arthritis, to name a few.

For instance, according to the Symes abstract, "[s]ustained expression of the growth factor product from somatic cells transfected with the DNA for that protein has proven to be one of the major advantages of a gene therapy approach over administration of the protein." Symes further reports that several clinical trials based on intramyocardial injection of VEGF DNA in patients with otherwise inoperable coronary artery disease have recently been completed and "show the promise of being able to improve myocardial perfusion and reduce anginal symptoms in the majority of patients treated thus far."

According to the abstract by Herzog and Arruda, intramuscular injection of adeno-associated viral vector to patients with severe hemophilia B resulted in evidence of gene transfer to skeletal muscle and is now the subject of an ongoing clinical trial. In a canine model of hemophila, Monahan *et al.* also found that intramuscular gene delivery using rAAV vectors was safe and resulted in continued human Factor IX gene expression at ten weeks following vector administration.

Morini *et al.* found that intramuscular injection of an IL-12 expression vector produced significant, well-tolerated elevation of serum IL-12 levels and inhibited angiogenesis in NK cell-depleted and nude mice. Further, IL-12 plasmid DNA transfer

significantly prevented the growth and vascularization of highly angiogenic Kaposi's sarcoma and murine mammary carcinoma tumors in nude mice.

Song *et al.* recently reported that recombinant AAV-mediated AAT gene therapy by intramuscular injection prevented type 1 diabetes in NOD mice. This followed the report of Wang *et al.*, who achieved a significant reduction of blood glucose level in diabetic C57 mice following intramuscular injection of naked plasmid DNA encoding the human preproinsulin gene.

Cottard *et al.,* Kim *et al.*, Yang *et al.*, Dreja *et al. and Ijima* et al. all achieved successful results using a gene therapy approach on collagen-induced arthritis in mice. For example, Cottard *et al.* first showed transgene expression localized in deep muscle cells near the bone following injection of AAV-LacZ in mice, then achieved long term IL-4 expression persisting 129 days after intra-muscular injection of AAV-IL-4, with a significant reduction in disease characteristics. Kim *et al.* achieved protection against collagen-induced arthritis by intramuscular gene therapy using an expression plasmid for the IL-1 receptor antagonist and concluded that direct muscular injection of expression plasmid for IL-1Ra may effectively suppress the inflammatory pathology in arthritis. Dreja *et al.* found that injection of naked DNA encoding a truncated soluble Complement receptor 1 prevented the progression of collagen-induced arthritis.

Finally, Applicants have also submitted herewith abstracts by Prud'homme and Kessler *et al.*, each exalting the simplicity and efficacy of gene therapy by intramuscular injection. Given these reports and those discussed above, Applicants respectfully submit that the Nishikawa *et al.* reference cited in the Office Action is not representative of the state of the art with regard to gene therapy.

Given the documentary evidence submitted herewith regarding the success of gene therapy by injection in combination with the teachings of the '859 patent, and given the known correlation between the *in vitro* testing reported in the specification and *in vivo* activity, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 32 and 34 under §112, first paragraph.

Claims 36-38 stand rejected under 35 U.S.C. §112, first paragraph, as containing subject matter that was allegedly not described in the specification. Without necessarily agreeing with the rejection and in order to expedite allowance of the present application, Applicants have canceled claims 36-38 above. Accordingly, withdrawal of the rejection is respectfully requested.

This reply is fully responsive to the Office Action dated September 23, 2003. Therefore, a Notice of Allowance is next in order and is respectfully requested.

Except for issue fees payable under 37 CFR §1.18, the commissioner is hereby authorized by this paper to charge any additional fees during the pendency of this application including fees due under 37 CFR §1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 CFR §1.136(a)(3).

If the Examiner has any further questions relating to this Reply or to the application in general, she is respectfully requested to contact the undersigned by telephone so that allowance of the present application may be expedited.

Respectfully submitted,
MORGAN, LEWIS & BOCKIUS LLP

Michael S. Tosca
Reg. No. 43,210

Dated: March 23, 2004 By: _____
Bonnie Weiss McLeod, Ph.D.
Reg. No. 43,255

Customer No. 09629
Morgan, Lewis & Bockius LLP
1111 Pennsylvania Ave., NW
Washington, DC 20004
Tel: 202-739-3000
Fax: 202-739-3001